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Acid-catalyzed Reduction of Spirostanols and Spirostenols by Lithium Aluminum Hydride

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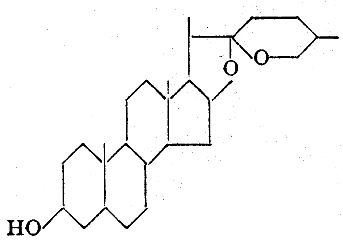
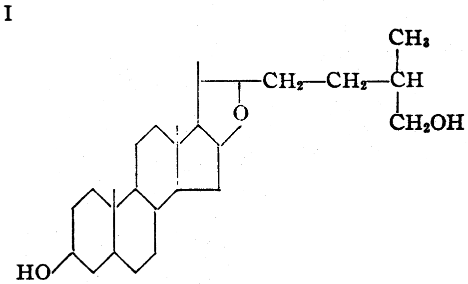
A new method for cleaving ring F of steroidal sapogenins with lithium aluminum hydride in the presence of anhydrous hydrogen chloride and hydrogen bromide is reported whereby furostene and furostane diols can be prepared directly from spirostenols and spirostanols.

The conversion of sapogenins (I) to their corresponding dihydro compounds II by catalytic hydrogenation under acid conditions was first reported by Marker and Rohrmann.[3]



I

$$\xrightarrow[\text{HAc, PtO}_2]{\text{H}_2}$$



II

Catalytic hydrogenation of diosgenin (22a,5-spirosten-3β-ol) always resulted in first the saturation of the double bond to tigogenin, followed by the opening of ring F to yield dihydrotigogenin (5α,22a-furostane-3β,26-diol). The Clemmensen method of reduction was also utilized by Marker and Rohrmann[3] to open simultaneously both oxido rings (E and F) in the spiroketal side chain to yield triol compounds.

The use of $LiAlH_4$ in opening oxido rings in the steroidal secondary amines, tomatidine[4] and solasodine,[5] has been reported but it was found that under the same alkaline reaction conditions neither oxido ring of steroidal sapogenins opened. It has been reported in an earlier Communication,[6] however, that $LiAlH_4$, in the presence of anhydrous HCl, reduces both spirostanols and spirostenols to their corresponding furostane and furostene diols. Further investigation of this new reaction using $LiAlH_4$ and $NaBH_4$ as reducing agents and several anhydrous acids (HCl, HBr, H_2S, SO_2, *p*-toluenesulfonic acid) have been completed. It was found that only $LiAlH_4$ in the presence of either HCl or HBr would open the oxido linkage.

It is well established that catalytic reduction of sapogenins in an acidic medium, using platinum oxide catalyst, results in a cleavage of ring F.[7] Therefore, diosgenin acetate was hydrogenated according to the method of Marker, *et al.*,[7] and the product acetylated to yield dihydrotigogenin diacetate (5α,22a-furostane-3β,26-diol 3,26-diacetate) (VI). The product obtained by this method was identical with the acetylated $LiAlH_4$ reduction product of tigogenin. That both rings E and F of sapogenins did not open under $LiAlH_4$ reduction is supported by the fact that the reduced compounds yielded only diacetyl products which showed the complete absence of an unacetylated hydroxyl group in the infrared spectra.

Infrared spectra, obtained on all compounds, were used as an aid in confirming the structure of the dihydro compounds. Wall, *et al.*,[8,9] and Jones,

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(2) Part of a Thesis presented by H. M. Doukas to the Georgetown University, Washington, D. C., in partial fulfillment of the requirements for the degree of Ph.D.

(3) R. E. Marker and E. Rohrmann, This Journal, **61**, 846 (1939).

(4) T. D. Fontaine, J. S. Ard and R. M. Ma, *ibid.*, **73**, 878 (1951).

(5) L. H. Briggs and R. H. Locker, *J. Chem. Soc.*, 3020 (1950).

(6) H. M. Doukas and T. D. Fontaine, This Journal, **73**, 5917 (1951).

(7) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, *ibid.*, **69**, 2167 (1947).

(8) M. E. Wall, C. R. Eddy, M. L. McClennan and M. E. Klumpp, *Anal. Chem.*, **24**, 1337 (1952).

(9) C. R. Eddy, M. E. Wall and M. K. Scott, *ibid.*, **25**, 266 (1953).

et al.,[10] have shown that the formation of dihydrosapogenin is associated with complete loss of the characteristic sapogenin side chain bands. The dihydrosapogenins produced by $LiAlH_4$ reduction, under acidic conditions, as well as by catalytic reduction using PtO_2, do not give the characteristic side chain peaks at either 10.14, 10.85, 11.1 and 11.75 μ or 10.18, 10.85, 11.1 and 11.55 μ.[8-10]

Experimental[11]

Dihydrodiosgenin (22a,5-Furostene-3β,26-diol) (III). By $LiAlH_4$–HCl Reduction.—Diosgenin (22a,5-spirosten-3β-ol) (1.0 g.), placed in a standard tapered 3-neck flask, equipped with an air-tight stirrer, a condenser with a $CaCl_2$ drying tube and a glass stopper, was dissolved in 500 ml. of anhydrous diethyl ether (over sodium) with stirring. The solution was saturated, at room temperature (25°), with anhydrous hydrogen chloride from a cylinder. Solid $LiAlH_4$, in pea-size amounts, was then added to the reaction mixture, with vigorous stirring, allowing sufficient time for each piece to react before an additional amount was added. After all the $LiAlH_4$ (3.0 g.) had been added, the reaction mixture was refluxed gently for 2 hours. An excess of HCl was maintained throughout the reaction. A few drops of water at a time were added until the excess $LiAlH_4$ was decomposed, then 100 ml. of water was added. A gray suspension appeared in the water layer but dissolved completely on standing overnight. The ether layer was separated from the water layer (acidic) and the water layer washed with additional amounts of ether. The combined ether fraction was washed with water, until neutral, then concentrated to dryness. The yield of product was 0.90 g. (90%). Recrystallized from acetone, the dihydrodiosgenin melted at 158–160°, $[\alpha]^{20}D$ −35° $CHCl_3$. Recrystallization of the dihydrosapogenins did not raise the melting points over 2°, thus indicating a high degree of purity of the crude products.

Acetylation of dihydrodiosgenin with acetic anhydride, with a few drops of pyridine present, at 25° yielded dihydrodiosgenin diacetate (22a,5-furostene-3β,26-diol 3,26-diacetate) (IV), m.p. 115–117° $[\alpha]^{20}D$ −39° $CHCl_3$.

(10) R. N. Jones, E. Katzenellenbogen and K. Dobriner, This Journal, **75**, 158 (1953); "Collected Infrared Absorption Spectra of Steroid Sapogenins," National Research Council of Canada and Sloan-Kettering Institute for Cancer Research, N.R.C. No. 2929 (1953).

(11) We are indebted to M. E. Wall, of this Laboratory, for supplying the spirostanols and spirostenol used in this work.

Anal. Calcd. for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66. Found C, 74.45; H, 9.73.

Dihydrotigogenin (5α,22a-Furostane-3β,26-diol) (V).—Tigogenin (5α,22a-spirostan-3β-ol) (1.0 g.) yielded 0.90 g. (90%) of crude V when reacting with $LiAlH_4$–HCl under the same conditions as in the preparation of III; recrystallized from acetone, m.p. 163–165° (lit. m.p. 167–170°,[7] $[\alpha]^{20}D$ −4° $CHCl_3$.

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08. Found: C, 77.41; H, 10.92.

Acetylation of dihydrotigogenin at 25° yielded dihydrotigogenin diacetate (5α,22a-furostane-3β,26-diol 3,26-diacetate) (VI), m.p. 116–117° (lit. m.p. 114–116° (7)), $[\alpha]^{20}D$ −15° $CHCl_3$.

Anal. Calcd. for $C_{31}H_{50}O_5$: C, 74.06; H, 10.03. Found: C, 74.15; H, 10.04.

Dihydrosarsasapogenin (22b-Furostane-3β,26-diol) (VII). (a) By $LiAlH_4$–HCl Reduction.—Sarsasapogenin (22b-spirostan-3β-ol) (1.0 g.) yielded 0.88 g. (88%) of crude VII when reacting under the same condition as in the preparation of III; recrystallized from acetone, m.p. 157–160° (lit. m.p. 165° (3)), $[\alpha]^{20}D$ −2° $CHCl_3$.

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08. Found: C, 77.45; H, 11.05.

Benzoylation of VII at 95° for one hour yielded a crystalline product, dihydrosarsasapogenin dibenzoate (22b-furostane-3β,26-diol 3,26-dibenzoate) (VIII); recrystallized from acetone, m.p. 95–97°.

Anal. Calcd. for $C_{41}H_{54}O_5$: C, 78.55; H, 8.68. Found: C, 78.37; H, 8.51.

Acetylation of VII with acetic anhydride yielded an oil which could not be crystallized, $[\alpha]^{20}D$ −5° $CHCl_3$.

(b) By $LiAlH_4$–HBr Reduction.—Sarsasapogenin (1.0 g.) was treated under the same conditions as in the preparation of III, except that the ether solution was saturated with anhydrous HBr gas, which had been passed through tubes of $CaCl_2$ and copper turnings to remove any trace of moisture and bromine. $LiAlH_4$ (3.0 g.) was added as before but the solution had to be resaturated with the anhydrous HBr before the addition was complete because the acidity decreased greatly as the hydride was added. After refluxing for 3 hours the material was worked up as for III; yield of crude VII 0.75 g. (75%); recrystallized from acetone, m.p. 158-161°; Br_2 absent.

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